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EXAMINER

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

Response to Amendment

1. The amendment filed 5/14/2009 has been entered and fully considered.
2. Claims 1-12, 14-16 are pending and have been fully considered.

Double Patenting

3. The terminal disclaimers filed on 5/14/2009 for copending applications 10/588,695 and 10/588,696 have been reviewed and are accepted. The terminal disclaimers have been recorded.

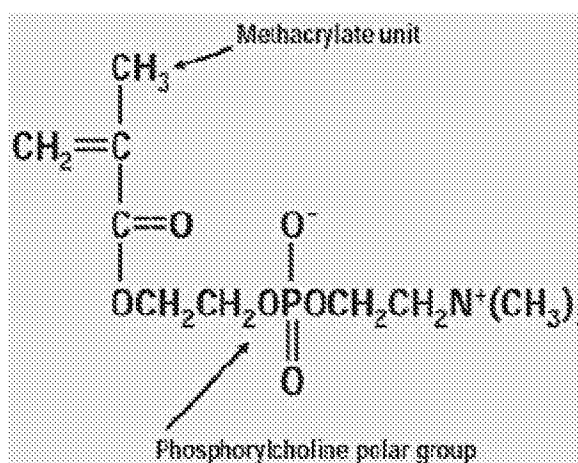
Claim Rejections - 35 USC § 102/103

4. Claims 1, 4, 8-12, 14, 16 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US PG Pub 2004/0045897, NAKABAYASHI et al. (where the PCT Publication WO02/09857 and EP 1 306 121 are related 102(b) date references) as evidenced by Developments in Medical Polymers for Biomaterials Applications, KATZ.

As to Claims 1, 11, NAKABAYASHI discloses a process for producing a porous substrate (Abstract), comprising: preparing a casting solution of polymer and solvent; conversion of the solution into a shaped object with a first and second surface (Ex. 1-8); bringing the inner surface into contact with a precipitant system resulting in the formation of a separating layer on the inner surface (Pg. 2, Para. 15); and washing (Ex. 1-8); wherein the precipitant system includes MPC copolymer (2-methacryloyloxyethyl

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phosphorycholine), which contains a fixed negative charged group as evidenced by KATZ (shown below). The MPC co-polymer is zwitterionic and therefore has a net zero charge and may not expressly disclose the negatively fixed charge of the polyelectrolyte. However, NAKABAYASHI discloses inclusion of vinyl-polymerizable monomer (Formula 3, Pg. 3, Para. 23) wherein R8 is a hydrogen atom (negatively charged group) is polymerized with MPC and injected in the inner lumen (Ex. 1-8). Therefore, in the alternative the MPC co-polymer with the negatively charged polymerizable monomer (Formula 3) that is injected in the hollow fiber at least renders obvious the polyelectrolyte with negative charge in the precipitant system.



As to Claim 4, NAKABAYASHI discloses that the dissolved interior filler precipitates in contact with the spinning solution (Ex. 1-8), for the purposes of clarification, this occurs as the spun raw material is passed through a water bath, the resulting hollow fiber has a MPC copolymer concentration in the inner lumen – this is stated below in Example 1.

EXAMPLE 1

[0048] 18 parts of polysulfone ("Ultrason S3010" manufactured by BASF) was added to a mixture of 57 parts of N,N-dimethylacetamide (DMAC) and 25 parts of tetraethylene glycol (TEG). The mixture was stirred for 6 hours at 60° C. and dissolved to obtain a membrane-forming raw material solution. The raw material solution maintained at a temperature of 45° C. was discharged from spinnerets with an annular orifice together with a 40% aqueous solution of DMAC, to which 1% of a copolymer of MPC and methacryloyloxyethyl phenyl carbamate (MPC monomer unit content=0.31, molecular weight=109,000) was added as an internal coagulate solution. The spun raw material was passed through a water bath, placed 36 cm lower than the discharge nozzle, at 55° C. to be wound around a reel, and washed with hot water at 90° C. to remove any excess copolymer and the solvent. The resulting hollow fiber membrane was confirmed to have a water permeability of 325 ml/m²-mmHg-hr, an MPC copolymer concentration on the inner side surface of 13 wt %, and a bulk concentration of 0.25 wt %. The absorbance of the extract obtained from the hollow fiber membrane determined by the elution material measurement method was 0.020.

As to Claims 8-9, NAKABAYASHI discloses polysulfone polymer used as the membrane-forming polymer (Pg. 3, Para. 22).

As to Claim 10, NAKABAYASHI discloses the forming device is a hollow fiber die, which converts the spinning solution into a hollow-fiber with an inner and outer side (Ex. 1-8).

As to Claim 12, NAKABAYASHI discloses an integrally asymmetric membrane with a separating and supporting layer (Abstract, Pg. 3, Para. 15) comprising an interior filler comprising a negatively charged polyelectrolyte (MPC) wherein the outer layer is free from the interior filler (Ex. 1-8) and interior filler is physically bound in the separating layer (Pg. 4, Para. 36-37). The MPC co-polymer is a zwitteronic and has a net zero charge and may not expressly disclose the negatively fixed charge of the polyelectrolyte. However, NAKABAYASHI discloses inclusion of vinyl-polymerizable

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monomer (Formula 3, Pg. 3, Para. 23) wherein R8 is a hydrogen atom (negatively charged group) that polymerizes in the inner lumen dynamically during injection (Ex. 1-8). Therefore, in the alternative the MPC co-polymer with the negatively charged monomer (Formula 3) that is polymerized during injection at least renders obvious the polyelectrolyte with negative charge in the precipitant system.

As to Claim 14, NAKABAYASHI discloses that the separating layer faces the lumen (Claim 9, Pg. 6-7, Para 36-38), where it is implicit that the inner solution coagulates the membrane faster than air resulting in an inner separating layer.

AS to Claim 16, NAKAGASHI discloses that the membrane is chemically modified with an agent that reacts with the polyelectrolyte with negative fixed charges (Pg. 4-5, Para. 40-41).

Claim Rejections - 35 USC § 103

5. **Claims 1-12, 14-16 are rejected under 35 USC 103 (a) as being obvious over US Patent No. 4,604,208, CHU et al. in combination with US PG Pub 2004/0045897, NAKABAYASHI et al. (where PCT Publication WO02/09857 and EP 1 306 121 are related 102(b) date references) as evidenced by Developments in Medical Polymers for Biomaterials Applications, KATZ.**

As to Claims 1-3, 11, CHU discloses a process for producing a negatively charged microporous filter membranes (Abstract, C8/L16-18), comprising: preparing a casting solution of polymer and solvent (C7/L34-37); conversion of the solution into a shaped object with a first and second surface (C8/L34-38); extrusion over a fluid core

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(C8/L34-38); and washing (C8/L30-32). CHU discloses extrusion over a fluid core but does not specify the precipitant system brought into contact with the inner surface.

However, NAKABAYASHI discloses bringing the inner surface into contact with a precipitant system resulting in the formation of a separating layer on the inner surface (Pg. 2, Para. 15), where the precipitant system includes MPC copolymer (2-methacryloyloxyethyl phosphorycholine), which contains a negatively charged group as evidenced by KATZ (shown above) and the inclusion of vinyl-polymerizable monomer (Formula 3, Pg. 3, Para. 23) where R8 is a hydrogen atom (negatively charged group) that polymerizes in the inner lumen dynamically during injection (Ex. 1-8).

NAKABAYASHI does not appear to expressly disclose a negatively charged polyelectrolyte in the inner fluid (as the MPC co-polymer is zwitteronic and the monomer polymerizes during injection). However, CHU discloses applying an anionic charge modifying agent to a filter membrane (Abstract) where the anionic charge modifying agent is polyelectrolyte, specifically polyacrylic acid (C12/L56-C13/L17, C10/L35).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify the teaching of CHU for making the membrane with the teaching of Nakabayashi and include the polyelectrolyte of CHU in the "core liquid" of Chu, as in the inner fluid precipitant system of NAKABAYASHI. The suggestion would have been to improve the efficiency of the process by discharging a modifying agent in the inner lumen during the production of the membrane (Pg. 2, Para. 15) thereby reducing the number of steps. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

As to Claim 4, NAKABAYASHI discloses that the dissolved interior filler (MPC and DMAC) precipitates in contact with the spinning solution (Ex. 1-8), for the purposes of clarification, this occurs as the spun raw material is passed through a water bath, the resulting hollow fiber has a MPC copolymer concentration in the inner lumen – this is stated above in Example 1.

As to Claims 5-6, CHU discloses that the proportion by weight of the anionic polymer is at least 0.5% wt and should not exceed 10% wt (C12/L4-17), which overlap the ranges disclosed (0.01 to 10 wt % and 0.05 to 1 wt %).

As to Claims 7-9, NAKABAYASHI discloses polysulfone polymer used as the membrane-forming polymer (Pg. 3, Para. 22) and CHU discloses cellulosic polymer (C7/L22-29) as the membrane-forming polymer.

As to Claim 10, NAKABAYASHI discloses the forming device is a hollow fiber die, which converts the spinning solution into a hollow-fiber with an inner and outer side (Ex. 1-8).

As to Claim 12, CHU discloses a hollow fiber with a supporting and separating layer (C8/L34-38) comprising a polyelectrolyte with a fixed negative charge physically bound on the membrane (C12/L40-48, C10/L35). CHU does not appear to expressly disclose that the supporting layer is free from polyelectrolyte. However, NAKABAYASHI discloses interior filler where the outer layer is free from the interior filler (Ex. 1-8) and interior filler is physically bound in the separating layer (Pg. 4, Para. 36-37).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify the hollow fiber membrane of CHU to include the supporting layer free

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from interior filler of NAKABAYASHI. The motivation would have been to have a high performance biocompatible membrane with hydrophobicity maintained on a portion of the membrane by having it free from interior filler (Pg. 2, Para. 10, Pg. 1, Para. 4). Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

As to Claim 14, NAKABAYASHI discloses that the separating layer faces the lumen (Claim 9, Pg. 6-7, Para 36-38), where it is implicit that the inner solution coagulates the membrane faster than air resulting in an inner separating layer.

As to Claim 15, CHU discloses that the membrane separates cationic contaminants (C14/L37-53), which implicitly includes proteins, absent evidence to the contrary.

As to Claim 16, NAKABAYASHI discloses that the membrane is chemically modified with an agent that reacts with the polyelectrolyte with negative fixed charges (Pg. 4-5, Para. 40-41) and CHU discloses the application of an anionic charged modifying agent (polyelectrolyte) and crosslinking agent to modify the membrane to have negative charges (C13/L32-51, Claim 1).

Response to Arguments

6. Applicant's arguments with respect to claims 1-12, 14-16 filed 5/14/2009 have been fully considered but are not persuasive.

Applicant's arguments addressing the zwitterionic compound of NAKABAYASHI are not persuasive. Examiner holds that while the compound has a net zero charge, the

zwitterionic negative charge on the compound renders the application at a minimum obvious and in the alternative anticipatory.

Applicant argues that the examiner has misunderstood the nature of the reference NAKABAYASHI. For the purpose of clarity, Examiner's position has been clarified in the rejection of Claim 4 and below. Example 1 discloses that the co-polymer is discharged in the inner lumen as an internal coagulate solution, and the resulting hollow fiber membrane has an inner side with a immobilized concentration of the copolymer after immersion in the water bath. Various methods of ensuring the inclusion of the co-polymer in the hollow fiber are disclosed also in Pg. 5, Para. 44.

EXAMPLE 1

[0048] 18 parts of polysulfone ("Ultrason S3010" manufactured by BASF) was added to a mixture of 57 parts of N,N-dimethylacetamide (DMAC) and 25 parts of tetraethylene glycol (TEG). The mixture was stirred for 6 hours at 60° C. and dissolved to obtain a membrane-forming raw material solution. The raw material solution maintained at a temperature of 45° C. was discharged from spinnerets with an annular orifice together with a 40% aqueous solution of DMAC, to which 1% of a copolymer of MPC and methacryloyloxyethyl phenyl carbamate (MPC monomer unit content=0.31, molecular weight=109,000) was added as an internal coagulate solution. The spun raw material was passed through a water bath, placed 36 cm lower than the discharge nozzle, at 55° C. to be wound around a reel, and washed with hot water at 90° C. to remove any excess copolymer and the solvent. The resulting hollow fiber membrane was confirmed to have a water permeability of 325 ml/m²·mmHg·hr, an MPC copolymer concentration on the inner side surface of 13 wt %, and a bulk concentration of 0.25 wt %. The absorbance of the extract obtained from the hollow fiber membrane determined by the elution material measurement method was 0.020.

[0044] Various known methods of manufacturing hollow-fiber membranes can be used for previously preparing the hollow-fiber membrane to be modified. Any synthetic polymers to which these membrane-forming methods are applicable can be used as the material for forming the hollow-fiber membrane. In this method, a solution for adsorption treatment prepared by dissolving the MPC copolymer in a suitable solvent is caused to come into contact with the membrane surface on which the MPC copolymer should be unevenly distributed, thereby causing the MPC copolymer to be adsorbed. The MPC copolymer can be adsorbed using any appropriate method such as a method of immersing the hollow fiber into the adsorbed solution, a method of passing the adsorbed solution through the hollow space or outside the hollow-fiber membrane, or a method of encapsulating the adsorbed solution into the hollow space or outside the hollow-fiber membrane. After that, excess copolymer and solvent are removed by washing. Then, the product is dried, if necessary. These processing can be carried out either in the module step when the hollow fiber has been formed or in the step before formation of the hollow fiber. The concentration of the MPC copolymer in the adsorbed solution in the range of 0.001-10 wt % is sufficient for attaching the MPC copolymer to the membrane surface necessary for the hollow-fiber membrane to exhibit biocompatibility, with the range of 0.01-5 wt % being more preferable.

Applicant argues that there is no motivation to combine CHU and NAKABAYASHI, this is not found persuasive as a clear motivation is articulated in the rejection above and further it would be obvious to one of ordinary skill in the art to use

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the teachings of these references to arrive at applicant's invention because it produces no more than predictable results. See *KSR Int'l. v. Teleflex Inc.*, 127 S. Ct. 1727, 1732, 82 USPQ2d 1385, 1390 (2007). "it is commonsense that familiar items have obvious uses beyond their primary purposes, and a person of ordinary skill often will be able to fit the teachings of multiple patents together like pieces of a puzzle". "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results". Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Regarding the rejection of Claim 16, for the purposes of clarification, NAKABAYASHI discloses the MPC co-polymer is dissolved in a solution of non-solvent and solvent, the amount solvent and non-solvent can be varied to modify performance (Pg. 5, Para. 40-41), this is chemical modification with an agent. Further, the recitation of "the membrane being for chemical modification with an agent that reacts with the polyelectrolyte" relates to intended use and it has been held that a claim containing a "recitation with respect to the manner in which a claimed apparatus is intended to be employed does not differentiate the claimed apparatus from a prior art apparatus". *Ex parte Masham*, 2 USPQ2d 1647 (Bd. Pat. App. & Inter. 1987). Further, CHU discloses chemical modification as shown in the rejection above.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208

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USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Conclusion

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: US Patent No. 5,919,370 provides evidence that the precipitant in the inner filling creates the internal separating layer of the hollow fiber.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARJORIE CHRISTIAN whose telephone number is (571)270-5544. The examiner can normally be reached on Monday through Thursday 7-5pm (Fridays off).

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vickie Kim can be reached on (571)272-0579. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Krishnan S Menon/
Primary Examiner, Art Unit 1797

MC